New Drugs

Modern diuretic treatment

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Diuretics are one of the most widely prescribed group of drugs with therapeutic indications in a diverse set of disorders.

Oedema

Thiazide diuretics form the mainstay of treatment for numerous conditions characterised by oedema, most notably congestive heart failure when there is a reduced glomerular filtration rate, increased aldosterone production, and increased sodium reabsorption from the renal tubules. Longstanding heart failure no longer responsive to a thiazide often responds dramatically to a loop diuretic, and a loop diuretic also rapidly relieves acute pulmonary oedema secondary to left ventricular failure. Resistant oedema, on the other hand, may respond favourably when diuretics that act on different parts of the renal tubule are given together—for example, thiazide plus a loop diuretic with or without the addition of an aldosterone antagonist. A thiazide or loop diuretic is prescribed together with spironolactone in the nephrotic syndrome and in cirrhosis of the liver complicated by ascites, both conditions being almost invariably associated with secondary hyperaldosteronism.

Thiazides and spironolactone are often prescribed, too, in some cases of recurrent, idiopathic cyclical oedema, particularly of the ankles, associated with water retention. In this disorder, which is most often seen in premenopausal women and especially at menstruation, diuretics may have an initial cosmetic effect, but long term benefit is hard to establish. Thiazides are also often inappropriately prescribed in managing chronic lymph-oedema or chronic ankle oedema associated with varicose veins and poor venous return. Only in a few of these patients is the oedema easier to control as a result of using diuretics; adequate elastic support is more appropriate.

The requirement for diuretic treatment in managing oedema needs to be regularly reassessed in order not to exceed the necessary minimum dose of the least powerful diuretic that will suffice. When clinical judgment does not suffice, a useful means of measuring the loss of sodium and water is to observe the rate and extent of weight loss. Provided that the serum sodium concentration remains normal, 1 kg of water loss corresponds to 140-150 mmol(mEq) of associated sodium loss. Another useful assessment is to measure the 24 hour urinary sodium excretion: if this is below 10-20 mmol the diuretic treatment is inadequate, but if it is quite high (above 100 mmol) and body weight is not decreasing sodium excretion is satisfactory but sodium intake needs to be reduced. On the other hand, some patients are at risk of developing saline depletion with loss of tissue turgor, postural hypotension, and a rising serum urea concentration because of loss of interstitial fluid and a fall in plasma volume with poor renal perfusion. The diuretic dose in such patients may best be adjusted to allow mild ankle oedema in the evening, which will clear during the night in bed. Excessive diuresis will otherwise produce undue shrinkage of the plasma volume with resultant secondary hyperaldosteronism and hypokalaemia. Excessively rapid clearance of oedema also causes malaise.

Hypertension

Until now thiazides have remained one of the cornerstones of antihypertensive treatment in patients with normal renal function, but their long term metabolic consequences are beginning to cause increasing concern. Loop diuretics are generally less effective than thiazides in lowering the blood pressure in all but the more severe forms of hypertension and those associated with renal impairment. Small doses of thiazides lower blood pressure in both the erect and supine positions and only rarely cause postural hypotension. They are often used alone or are given together with other classes of antihypertensive drugs. They are particularly effective in patients with low renin hypertension—for example, many older patients and blacks—but their effect may not be apparent for two to three days and their maximum effect may not be reached for two to three weeks. The hypotensive effect of diuretics is not related solely to the initial fall in plasma volume but also to a later decrease in peripheral vascular resistance with long term treatment and possibly an effect on prostaglandin synthesis in the kidney. The antihypertensive effect of the thiazide diuretics is not much increased by increasing the dose—that is, they have a fairly flat dose-blood pressure response curve—but metabolic side effects become more troublesome with increasing dosage.

Other uses

Intravenous loop diuretics, often given together with a thiazide, increase the excretion of calcium in patients with hypercalcaemia. Thiazides alone have an established role in the management of idiopathic hypercalciuria associated with recurrent renal calculi in which they may decrease the urinary calcium output by as much as 40% at the expense of a slight increase in the serum calcium concentration. Long acting thiazides are used in the nephrogenic form of diabetes insipidus: their efficacy here may in part be related to the loss of sodium by the kidney, causing a decreased delivery of filtrate to the diluting segment of the renal tubule. Loop diuretics are also important in managing certain cases of acute or chronic renal failure. In acute renal failure, for example, high dose intravenous frusemide produces an effective diuresis in about a third of patients with a consequent reduced need for dialysis.

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Classification

There are three main classes of diuretic in common use—thiazides and related compounds, loop diuretics, and potassium sparing diuretics. Clinically they are more usefully considered as medium, high, and low potency diuretics respectively. These are discussed in detail below.

THIAZIDES AND RELATED COMPOUNDS

Thiazide diuretics are rapidly absorbed from the gastrointestinal tract and most produce a demonstrable diuresis within one to two hours after ingestion and are excreted unchanged in the urine. They act in the cortical portion of the ascending tubule and at the beginning of the distal convoluted tubule, where under 10% of the filtered sodium load is reabsorbed, and so cause excretion of only 5-10% of this sodium load. Of the several generic preparations available, all are equally effective if equivalent doses are given, but their duration of action differs. Hydroflumethiazide is one of the shortest acting and although the action of most thiazides such as bendrofluazide is complete within 10-12 hours, others have a much longer duration of action and so may be given on alternate days (see table). A short acting preparation taken once only early in the day will usually alleviate troublesome nocturia, which is sometimes associated with longer acting preparations.

SIDE EFFECTS

Hypokalaemia, which tends to be intermittent, especially in hypertensive patients, is the best known side effect of long term continuous thiazide treatment. A noticeable decrease in serum potassium concentrations occurs in 30-50% of patients. It is dose related and therefore often seen in those with a pronounced or prolonged diuresis, but it does not necessarily reflect a similarly significant drop in total body potassium stores. Hypokalaemia is nearly always asymptomatic unless the serum potassium concentration falls below 2·5 mmol(mEq)/l and it therefore needs to be sought, especially in those receiving a cardiac glycoside, because of the enhanced risk of serious cardiac arrhythmias. There is increasing evidence, too, that when acute cardiac infarction supervenes in patients who are already hypokalaemic the risk of serious ventricular arrhythmias is increased about twofold and death from ventricular fibrillation almost fivefold. Adrenaline mediated augmentation of this hypokalaemia may play an important part in this risk. Diuretic induced hypomagnesaemia seems also to increase the incidence of cardiac arrhythmias. If this work is substantiated much greater attention will be required to try to reduce these risks. Hypokalaemia may also precipitate hepatic encephalopathy and coma in those with liver cell failure. Hyperuricaemia, which is probably caused by enhanced tubular reabsorption of urate, occurs in about 40% of men receiving long term thiazide treatment but is less common in women. This hyperuricaemia is persistent throughout thiazide treatment, but in the absence of gout it is probably harmless and no treatment is required. Indapamide, spironolactone, and bumetanide have a lower propensity to cause hyperuricaemia. Impaired glucose tolerance occurs so slowly that it is not normally of any clinical importance even in diabetics, in whom it is rare for changes in diet or increased doses of an oral hypoglycaemic agent or insulin to be required. If necessary a thiazide may be used together with a potassium sparing diuretic or ethacrynic acid as these are less likely to upset diabetic control. Increasing concern has been voiced that raised lipoprotein, triglyceride, and total cholesterol concentrations with a fall in high density lipoprotein cholesterol produced by thiazides may increase the risks of coronary heart disease during long term treatment, but in hypertension, at least, the benefit in terms of reduced incidence of stroke alone still far outweighs these largely theoretical worries. None the less, beta-blockers are increasingly seen as preferable first line drugs in managing essential hypertension. They, too, are not free from metabolic side effects, but adequate data are not yet available for comment. The most recently recognised side effect in young hypertensive men receiving long term thiazide treatment is a high incidence of impotence, which is reversible within a few weeks of withdrawing the drug. Thiazides, because they decrease sodium reabsorption in the proximal tubules indirectly, increase reabsorption of lithium with the consequent danger of inducing lithium toxicity in those with mania receiving long term treatment with lithium.

NEW DRUGS

Indapamide is chemically related to chlorthalidone and is claimed to lower blood pressure in most patients as effectively as thiazides but with little diuresis unless the dose exceeds 2·5 mg/day. Slight loss of weight associated with pronounced diuresis sometimes occurs in the elderly. The drug may have a useful role in managing hypertension in patients with prostatism or an unstable bladder, but it is not used to treat oedema. In contrast to the thiazides, indapamide has little or no apparent influence on concentrations of serum potassium, uric acid, glucose, or lipoproteins and produces only a modest rise in plasma renin activity; rashes may occur. Indapamide may, however, have an additional effect of decreasing the initial calcium current in arterial smooth muscle, and there has been a claim that resistant hypertension may be improved on long term use of the drug, presumably through a vasodilator action. In practice, no clear advantage of this expensive new drug over the established thiazides has yet been consistently shown, and further studies are required before its proper therapeutic role can be confidently defined.

Xipamide is a salicylate derivative which also structurally resembles chlorthalidone but it too has very different effects, being neither a thiazide nor a specific loop diuretic. It is marketed for use both in hypertension and for the "gentle" control of oedema in the elderly, but may be more potent than thiazides in both conditions. In hypertension once daily administration has comparable efficacy to that of beta-blockade over 24 hours without producing postural hypotension, but many elderly patients find its rather intense and prolonged diuresis disturbing. Although when it was first introduced in the United Kingdom side effects were reported as uncommon, hypokalaemia, sometimes profound and in part dose related, has emerged as the most worrying aspect of its long term use in some patients. Regular serum potassium estimations are therefore necessary if the drug is used long term, and the concurrent prescription of a potassium sparing diuretic often becomes desirable. Further work is again necessary with this compound before its role in modern diuretic treatment may be properly assessed.

LOOP DIURETICS

Loop diuretics (table) are rapidly and completely absorbed from the gut and consequently have an abrupt onset of action with the attainment of peak plasma concentrations at about 1·5 hours after ingestion. All are highly bound to plasma proteins. Bumetanide is excreted together with its metabolites in the urine. Frusemide is eliminated mainly unchanged in the tubules except in those patients with a glomerular filtration rate of below 10 ml/min, in whom gut excretion becomes important. Ethacrynic acid is extensively metabolised, and both the metabolites and the parent drug are excreted mainly in the urine.

Loop diuretics are powerful drugs because they inhibit sodium reabsorption from the ascending limb of the loop of Henle in the renal tubule where normally about 20% of the filtered sodium is reabsorbed, with, in addition, weak effects in the proximal tubule and the cortical diluting segment. Unlike the thiazides,

Some thiazides, related drugs, and other commonly used diuretics

Name (proprietary name)	Recommended oral daily dose	Duration of action
Thiazides:		
Bendrofluazide (Aprinox, Berkozide, Centyl, Neo-NaClex, Urizide)	5 mg (hypertension) 10 mg (heart failure)	10–12 hours
Chlorthalidone (Hygroton)	12·5–25 mg (hypertension)	2–3 days
Hydroflumethiazide (Hydrenox)	50 mg (heart failure)	4–6 hours
Metolazone (Metenix)	5–20 mg (heart failure)	18–25 hours
New drugs:		
Indapamide (Natrilix)	2·5 mg (hypertension)	4–6 hours
Xipamide (Diurexan)	20 mg (hypertension) 20–40 mg (heart failure)	3–12 hours
Loop diuretics:		
Bumetanide (Burinex)	0·5–2 mg daily or twice daily (heart failure); 5 mg in oliguria	4–6 hours
Frusemide Aluzine (Dryptal, Frusetic, Frusid, Lasix)	20–80 mg daily or twice daily (heart failure); up to 2 g in oliguria	4–5 hours
Potassium sparing diuretics:		
Spironolactone (Aldactone, Diatensec, Spiroctan)	50–200 mg	3–5 days } Peak effect diuresis
Amiloride (Midamor)	5–20 mg	4–5 hours } continues for
Triamterene (Dytac)	50–200 mg	8–12 hours } 2–3 days

loop diuretics have an infinite dose response curve and so may cause excretion of up to 30% of the filtered sodium load. They remain effective diuretics even when the glomerular filtration rate is as low as 10 ml/min, but large doses are usually then required. This also makes them potentially more dangerous as the diuresis is proportional to the dose even in the face of volume and electrolyte depletion. Bumetanide may sometimes appear more potent than frusemide. After ingestion both drugs produce an effective diuresis within half an hour, the diuresis lasting between four and six hours. Intravenous administration produces a more rapid onset of action with peak diuresis occurring within 30 minutes, and it also produces an even more prompt fall in left ventricular filling pressure due to changes in venous capacitance, which in turn explains the particular use of these drugs in acute left ventricular failure. The action of ethacrynic acid is similar but it lasts for six to eight hours and is occasionally useful when the patient is refractory to either bumetanide or frusemide. In the elderly, however, there is an increased incidence of postural hypotension and dizziness. The main use of loop diuretics is therefore in the management of acute left ventricular failure, resistant oedema as in cirrhosis or the nephrotic syndrome, resistant hypertension, and in oliguric renal failure.

Side effects

Side effects of the loop diuretics are largely dose related. Hypovolaemia with hypotension and later hyponatraemia is always a hazard. Hypokalaemia occurs much less often than with the thiazides except when twice daily dosage is used, there being a 25-30% incidence with long term use. Unlike the thiazides they do not cause hypercalcaemia but rather they enhance the excretion of calcium. Like the thiazides, the loop diuretics may have a minor effect on glucose tolerance and cause hyperuricaemia with the occasional precipitation of acute gout, especially by frusemide. Brumetanide causes less magnesium loss than frusemide when taken long term. Loop diuretics should be used with caution in liver failure because of the risk of inducing hepatic coma. Loop diuretics may cause urinary incontinence in the elderly and precipitate acute urinary retention in those with an enlarged prostate. Some patients experience loin pain during the abrupt diuresis, but the shortness of the diuresis allows twice daily usage without interference with sleep. Gastrointestinal upset and sensitivity reactions may occur, as with the thiazides, and bullous rashes, although rare, may occur when high doses are used in renal failure. Ethacrynic acid, unlike frusemide and bumetanide, is not a sulphonamide derivative and exhibits no cross sensitivity with the thiazides. Temporary deafness and tinnitus may follow the use of all three loop diuretics in renal failure.

Several important drug interactions may occur with the loop diuretics. Frusemide, for example, may enhance the nephrotoxic effects of certain antibiotics such as gentamicin, and it may also cause sweating, hot flushes, tachycardia, and variable changes in blood pressure in those receiving chloral hydrate. Ethacrynic acid may increase the anticoagulant effect of warfarin. As with the thiazide diuretics, certain non-steroidal anti-inflammatory drugs such as indomethacin, and also carbenoxolone, steroids, and oestrogens—for instance, the pill—all cause salt retention and antagonise the action of the loop diuretics.

POTASSIUM SPARING DIURETICS

Although potassium sparing diuretics are only weak diuretics, they potentiate the action of the thiazides or loop diuretics and are commonly used in combination to promote potassium retention. They act on the distal tubule, but only spironolactone and potassium canrenoate antagonise aldosterone. These two are particularly useful when there is excess circulating aldosterone, either primary (Conn's syndrome) or secondary, as in liver cirrhosis or the nephrotic syndrome, or occasionally in the oedema of resistant heart failure. In heart failure, when high dose frusemide—for example, 160 mg—proves inadequate, it is better to add spironolactone, especially if the 24 hour urinary sodium:potassium ratio is under 1·0, as increasing the loop diuretic dosage leads to loss of potassium rather than sodium in the urine. They are all expensive but maintain serum potassium concentrations much more reliably than does the use of low dose potassium supplements.

Canrenone, the active metabolite of spironolactone, has a much longer half life (about 10 hours) than the other two agents. While amiloride and triamterene may have a more rapid onset of effect, spironolactone may produce a greater potassium sparing effect. Since these drugs are used mainly because of their potassium sparing rather than their diuretic or antihypertensive properties, they are often prescribed as a combined thiazide-potassium sparer preparation—for instance, Aldactide, Moduretic, Dyazide.

Side effects

All these drugs promote potassium retention and therefore must be avoided or used with great caution when there is evidence of renal impairment because of the risk of hyperkalaemia and must never be prescribed together with potassium supplements. Tender nipples or painful gynaecomastia, menstrual irregularities, hirsuitism, and impotence are problems, particularly of large doses and long term treatment with spironolactone, and stem from the steroid configuration of the drug. Other less common side effects of these drugs include gastrointestinal upsets, especially nausea, epigastric discomfort, and diarrhoea, and mental confusion, chloasma, and rash. Potassium canrenoate causes nausea and vomiting especially in high dosage.

OTHER DIURETICS

Carbonic anhydrase inhibitors such as acetazolamide still have a use in glaucoma, albeit a diminishing one, and they have been tried in the prophylaxis of mountain sickness. Osmotic diuretics such as mannitol (Osmitrol) are commonly used to produce a forced diuresis in patients with cerebral oedema or self poisoning with drugs. The 20% solution of mannitol may also produce a useful diuresis in oedema resistant to other diuretics, and it is also used to prevent renal failure in jaundiced patients undergoing surgery. Osmotic diuretics are contraindicated in renal or hepatic failure and in patients who have sustained a recent cerebral haemorrhage. It is less well known that isosorbide acts as a well tolerated orally active osmotic diuretic and has occasional use in lowering raised intracranial or intraocular pressure and in helping to clear hepatic ascites resistant to other measures.

POTASSIUM SUPPLEMENTS

Potassium chloride preparations are overprescribed since they are not usually necessary in patients receiving small doses of diuretics and in most young ambulant hypertensive patients. The need for taking measures to maintain the serum potassium concentration may be minimised by using the smallest dose of diuretic necessary to control oedema, by using those diuretics intermittently when possible, and by restricting unnecessary intake of salt. A more careful appraisal of the need for conserving potassium may, however, be needed in a few selected clinical conditions—for example, in the elderly receiving long term diuretic treatment because of their usually poor dietary intake of potassium; those taking digoxin or any other cardiac glycoside or who show evidence of arrhythmias, recent cardiac infarction, or severe angina because of the hazards of serious ventricular arrhythmias (discussed earlier); those receiving other drugs that cause hypokalaemia—for instance, steroids—and in diabetics. In these conditions the addition of a potassium sparing diuretic is preferable to the high amounts of supplementary potassium, such as 64 mmol/day, usually required, particularly because long term patient compliance with the number of tablets required is likely to falter. Similarly, the use of a potassium sparing diuretic is preferable in those taking another drug that interferes with ventricular repolarisation such as prenylamine, phenothiazines, or a tricyclic antidepressant, whenever the serum potassium concentration falls below 3·5 mmol/l. When supplements are used, they are more effective when used as prevention than to correct pre-existing hypokalaemia when a potassium sparing diuretic is nearly always preferable. Finally, the widespread practice of using combined diuretic-potassium supplement preparations is difficult to justify: not only is the supplement seldom necessary but most preparations contain far too little potassium to meet the needs of those who are hypokalaemic, and most of this is lost from the kidneys while they are under the influence of the diuretic. When potassium supplements are chosen, it would seem preferable to give the diuretic first thing in the morning and the potassium supplement in a sufficiently large dose much later in the day; compliance with the number of tablets required remains a problem. In hypertension the addition of a beta-blocker or captopril will often negate the need for either a potassium sparing diuretic or potassium supplementation.

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What is the preferred method of sterilising vaginal speculae in general practice, particularly with regard to herpes virus? Can disposable plastic vaginal speculae be reused after appropriate sterilisation?

Most organisms, including the herpes virus, will be killed by 15 minutes' immersion in boiling water. Bacterial spores are resistant to boiling and require autoclaving for their eradication, but a small inoculum of anaerobic spore forming bacteria should not harm the healthy vagina, and boiling should be adequate for metal vaginal speculae in routine use. (Incidentally, a domestic pressure cooker can achieve the same result as an autoclave: after the cooker is brought to the boil an instrument should be steamed for 15 minutes at 15 lb/sq in—that is, the full pressure in an ordinary pressure cooker.) The difficulty with plastic speculae is finding an appropriate method of sterilisation. Most plastic speculae are not resistant to heat and therefore will warp or melt when boiled or autoclaved. Chemical methods of sterilisation are not necessarily effective against viruses and the chemicals may react with some plastics. These instruments are sterilised by gamma radiation, but repeated exposure to radiation weakens the plastic.—JAMES OWEN DRIFE, senior lecturer in obstetrics and gynaecology, Leicester.

Is mould on jam or cheese likely to be poisonous if eaten?

The appearance of mould on processed food is related to faulty processing or storage. Most of the moulds seen on jam and cheese are species of penicillium. Laboratory tests have shown that a substantial proportion of them are biologically active when tested in multiscreen systems for toxic secondary metabolites (mycotoxins). On this basis, therefore, ingestion of mouldy foodstuffs is potentially harmful. Although the extent of the risk is not known, and in most instances may be small, people should not eat mouldy food unless it has been deliberately moulded—for example, blue veined cheeses.—D W R MACKENZIE, director, PHLS Mycological Reference Laboratory, London.